Klinik für Reproduktionsmedizin

Abteilung für Grosstierreproduktion

der Vetsuisse-Fakultät Universität Zürich

Direktor Prof. Dr med. vet., Dipl. ECBHM Heinrich Bollwein

Arbeit unter wissenschaftlicher Betreuung von
Prof. Dr. med. vet., Dipl. ECBHM Ulrich Bleul

Doppler sonographic examination of uterine and placental perfusion in cows in the last month of gestation and effects of epidural anesthesia and isoxsuprine

Inaugural-Disseration

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

Cornelia Kim

Tierärztin
von Wettingen, Aargau

genehmigt auf Antrag von

Prof. Dr. med. vet., Dipl. ECBHM Ulrich Bleul, Referent

2015

Klinik für Reproduktionsmedizin

Abteilung für Grosstierreproduktion

der Vetsuisse-Fakultät Universität Zürich

Direktor Prof. Dr med. vet., Dipl. ECBHM Heinrich Bollwein

Arbeit unter wissenschaftlicher Betreuung von
Prof. Dr. med. vet., Dipl. ECBHM Ulrich Bleul

Doppler sonographic examination of uterine and placental perfusion in cows in the last month of gestation and effects of epidural anesthesia and isoxsuprine

Inaugural-Disseration

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

Cornelia Kim

Tierärztin
von Wettingen, Aargau

genehmigt auf Antrag von

Prof. Dr. med. vet., Dipl. ECBHM Ulrich Bleul, Referent

2015

Inhaltsverzeichnis

Summary

The goal of this study was to measure the perfusion of the uterine arteries and the placentomes in the last month of gestation and to investigate the effect of epidural anesthesia and isoxsuprine on perfusion. During the last month of gestation, 8 Braunvieh cows underwent 9 color Doppler sonographic examinations of the uterine arteries to determine diameter (DM), pulse rate (PR), resistance index (RI), time-averaged mean velocity (TAMV) and blood flow volume (BFV), and power-mode Doppler sonography was used to determine perfusion of placentomes. The PR increased, and the BFV and TAMV of the ipsilateral uterine artery decreased between 4.5 and 0.5 weeks prepartum.

After sonographic examination, the cows received epidural administration of local anesthetic lidocaine or isoxsuprine, and the sonographic measurements were repeated 30 min later. After epidural anesthesia, the TAMV and BFV of the contralateral uterine artery increased. In the placentomes of the gravid uterine horn, the relative placentome perfusion (rPP) and the color pixel grading (Cp) increased. After isoxsuprine the DM, PR and BFV increased in the ipsilateral and in the contralateral uterine artery. The TAMV of the ipsilateral uterine artery increased and the RI decreased in both uterine arteries. Isoxsuprine increased the rPP and the Cp of the placentomes in both horns.

Keywords: Gestation; Color Doppler ultrasound; Power Doppler Ultrasound; Uterine arteries; Placentomes

Zusammenfassung

Das Ziel dieser Studie war es, die Durchblutung in den Uterusgefässen und Plazentomen während des letzten Trächtigkeitsmonat zu quantifizieren und den Einfluss einer Epiduralanästhesie und Isoxsuprine auf die plazentäre Blutversorgung zu untersuchen. Im letzten Trächtigkeitsmonat wurden bei 8 Schweizer Braunviehkühen 9 Untersuchungen durchgeführt, wobei in den Aa. uterinae mittels Dopplersonographie der Durchmesser (DM), die Pulsfrequenz (PF), der Widerstandsindex (RI), die mittlere Blutflussgeschwindigkeit (TAMV) und das Blutflussvolumen (BFV) gemessen wurden. Der Blutfluss in Plazentomen wurde im Power Doppler Modus bestimmt. In der ipsilateralen A. uterina war 4.5 Wochen vor der Geburt die PF höher, das BFV sowie die TAMV tiefer als 0.5 Wochen vor der Geburt. Anschliessend an die sonographische Untersuchung erhielten die Kühe eine Epiduralanästhesie mit Lidocain oder Isoxsuprine intravenös, und die Messungen wurden 30 Minuten später wiederholt. Durch die Epiduralanästhesie erhöhte sich in der kontralateralen A. uterina die TAMV und das BFV und im graviden Horn die relative plazentomale Durchblutung (rPP) und die Blutflussmenge in den Plazentomen (Cp). Durch Isoxsuprine wurden der DM, die PF sowie das BFV in beiden Ae. uterinae erhöht. Zudem stieg die TAMV in der ipsilateralen A. uterina an und der Widerstandsindex sank in beiden Aa. uterinae. Der rPP und auch die Cp in den Plazentomen beider Hörner wurde erhöht.

Stichworte: Trächtigkeit; Color Doppler Ultraschall; Power Doppler Ultraschall; Uterine Arterien; Plazentome

Doppler sonographic examination of uterine and placental perfusion in cows in the last month of gestation and effects of epidural anesthesia and isoxsuprine

C. Kim-Egloff [1], M. Hässig [2], R. Bruckmaier [3], U. Bleul[1,*]

[1] Large Animal Reproduction Unit, Clinic for Reproductive Medicine, Vetsuisse-Faculty, University of Zurich, Switzerland

[2] Ambulatory and Stationary Clinic, Vetsuisse-Faculty, University of Zurich, Switzerland

[3] Veterinary Physiology, Vetsuisse-Faculty, University of Bern, Switzerland

* Corresponding author. Tel.: +41 44 6358253; fax: +41 44 6358904. E-mail address: ubleul@vetclinics.uzh.ch (U. Bleul).

Abstract

The massive increase in size of the fetus and uterus in the last trimester is accompanied by an increasing demand for nutrients and oxygen and it is assumed that this demand is met by increasing uterine and fetal perfusion. The goal of this study was to measure the perfusion of the uterine arteries and the placentomes in the last month of gestation and to investigate the effect of epidural anesthesia and isoxsuprine on perfusion. During the last month of gestation, 8 Braunvieh cows underwent 9 color Doppler sonographic examinations of the uterine arteries to determine diameter (DM), pulse rate, resistance index (RI), time-averaged mean velocity (TAMV) and blood flow volume (BFV), and power-mode Doppler sonography was used to determine perfusion of placentomes. The pulse rate increased ($P < 0.001$), and the BFV and TAMV of the ipsilateral uterine artery decreased between 4.5 and 0.5 weeks prepartum (BFV, 236.8 ± 65.80 and 208 ± 41.52 cm^3/s, $P < 0.01$; TAMV, 140.0 ± 26.53 cm/s and 125.2 ± 18.46 cm/s, $P < 0.05$).

After sonographic examination, the cows received epidural administration of local anesthetic (100 mg lidocaine) in the sacrococcygeal space or isoxsuprine (200 mg/cow, iv), and the sonographic measurements were repeated 30 min later. After epidural anesthesia, the TAMV and BFV of the contralateral uterine artery increased by 5.4 % ($P < 0.05$) and 7.9 % ($P < 0.01$). In the placentomes of the gravid uterine horn, the relative placentome perfusion (rPP) and the color pixel grading (Cp) increased by 10.1 % ($P < 0.05$) and 11.5 % ($P < 0.01$) after epidural anesthesia. After isoxsuprine the DM, pulse rate and BFV increased by 4.7 %, 49.3 % and 16.9 % in the ipsilateral uterine artery and by 10.8 %, 48.7 % and 22.8 % in the contralateral uterine artery. The TAMV of the ipsilateral uterine artery increased by 7.1 % ($P < 0.01$) and the RI decreased in both uterine arteries (ipsilateral 24.2 %, contralateral 14.9 %, both $P < 0.00001$).

Isoxsuprine increased the rPP and the Cp of the placentomes by 18.1 % and 18.3% in the gravid horn and by 10.2 % and 24.2 % in the non-gravid horn.
Blood flow variables changed little in the last month of gestation. However, epidural anesthesia and isoxsuprine caused changes in uterine and placentome perfusion that suggest improvement of placental nutrient and oxygen supply to the fetus.

Keywords: Gestation; Color Doppler ultrasound; Power Doppler Ultrasound; Uterine arteries; Placentomes; Intrauterine resuscitation

Introduction

The increasing fetal demand for nutrients and oxygen in the last trimester of gestation are met mainly through increased blood flow to the uterus, which in turn increases perfusion in the uterus [1]. In the past, invasive techniques were used to measure blood flow in the uterine arteries, which are largely responsible for uterine perfusion in cattle and horses [2, 3], but these techniques have been replaced by color Doppler sonography for transrectal measurement of uterine blood flow [4]. Color Doppler sonography has been used to measure blood flow variables in cycling cows as well as for quantification of uterine blood flow in pregnant cows and mares [4-7]. The resistance index (RI) decreased and time-averaged maximum velocity (TAMV), blood flow volume (BFV) and vessel diameter increased with advancing pregnancy in cows [4]. Another study showed that the birth weight of calves was positively correlated with blood flow volume [8].

The uterine arteries are mainly responsible for blood supply to the maternal placenta, and the umbilical arteries supply the fetal placenta. In addition to uterine blood flow, which was measured transrectally, fetal blood flow was measured transabdominally in an umbilical artery during the last few weeks of gestation [9], but no measurable changes in umbilical blood flow were detected in the last month of gestation. Another study measured umbilical blood flow during parturition using ultrasonographic transducers placed transvaginally on an umbilical artery and vein after rupture of the allantochorion [10]. Mean total blood flow was lower during the 60 min before delivery compared with the 30-min period before, and blood flow decreased transiently during uterine contractions. Furthermore, calves with a blood pH ≥ 7.2 immediately postnatum had a higher total blood flow in the last hour of gestation than calves with a pH < 7.2, which was interpreted as a direct effect of blood flow on placental gas exchange.

We are not aware of any reports on the direct measurement of placental circulation and specifically on blood flow in the placentomes, which prompted us to measure placental blood flow at the end of gestation using power-mode Doppler sonography. Color Doppler sonography describes blood flow based on the frequency shift of a flow volume, whereas power-mode Doppler sonography displays the strength of the Doppler signal in color by determining all moving particles in the blood, which allows recording of blood flow independent of blood flow velocity and direction. This is crucial for the quantitative and semiquantitative assessment of blood flow in tissues with low blood flow velocity and numerous blood vessels [11] such as placentomes. The goal of this study was to investigate whether blood flow in placentomes can be assessed quantitatively based on the size of the perfused area, and to what extent the color differences in the power-mode Doppler image are suitable for the semiquantitative determination of the number of all cells in the blood per unit of area.

Recently studies showed the effects of drugs on uterine and placental blood flow in cows [7, 9]. In human medicine, intrauterine resuscitative measures are employed to improve placental perfusion when abnormal fetal heart rate patterns are recognized with the goal of preventing fetal hypoxia and subsequent acidosis [12]. Two of these measures are the administration of a uterine relaxant drug and epidural anesthesia. We are not aware of any studies investigating the effect of such measures on placental perfusion in cows except for one investigation of changes in uterine perfusion induced by various drugs in the last month of gestation [9]. The latter study showed that the uterine relaxant drug isoxsuprine increased uterine blood flow volume by 5 % and epidural anesthesia by 6 %. Our hypothesis was that these two treatments also affect perfusion of the placentomes.

The purpose of the study was to increase our knowledge of Doppler sonographic changes in semiquantitative and quantitative blood flow variables in the uterine arteries and placentomes in the last month of gestation, and to determine the effect of isoxsuprine and epidural anesthesia on these variables.

1. Materials and methods

1.1. Cows

Eight Braunvieh cows, which ranged in age from 4 to 14 years and had normal singleton pregnancies, were used. Lactation numbers ranged from 3 to 11. The cows were admitted to our clinic one month before the calculated due date. They were kept in tie stalls, bedded with straw, and fed hay, grass silage and water ad libitum and had daily access to an exercise yard.

The use of animals for this study was approved by the cantonal veterinary office of Zurich (permit number 213/2010).

1.2. Study design,-B-mode, and Doppler sonography of the uterine arteries

The cows were examined twice a week by the same investigator (CK) starting one month before the calculated date of birth. In total 9 examinations per cow were included into the final analysis. After the clinical examination, both uterine arteries and the placentomes were examined sonographically using a portable ultrasound machine (LOGIQ e; General Electric Medical System, Glattbrugg, Switzerland). Transabdominal B-mode sonographic examination of the placentomes was carried out followed by transabdominal power-mode Doppler sonography using a 4-MHz convex probe (4C-RS, General Electric Medical System). Two placentomes in the gravid horn and one in the non-gravid horn were examined from the left and right ventral flanks cranial to the udder. The sites of examination were marked on the skin and kept constant for each cow. Scanning of the placentomes was repeated several times and the images were saved, and four measurements per placentome were then selected for analysis.

Transrectal B-mode and Color Doppler sonography of the ipsilateral (pregnant horn) and contralateral uterine arteries was then carried out using a 10-MHz linear probe (I739-RS, General Electric Medical System). Both uterine arteries were examined and identified as described [4, 5]. First, the external iliac arteries were identified at the point where they branch off the aorta. Following the external iliac artery ventrally, the uterine artery was identified crossing the external iliac artery. To confirm its identity, the uterine artery was followed dorsally toward the internal iliac artery until the *ligamentum teres vesicae* was encountered. This is the atrophied stump of the umbilical artery and allowed definitive identification of the uterine artery. The uterine artery was then traced back toward the uterus, and the point of measurement was located immediately cranial to the point where the uterine artery crossed the external iliac artery and vein. Measurements were repeated 3 to 5 times by temporarily removing the probe from the site of measurement and repositioning it. Transverse images of the uterine arteries were taken in B-mode for measuring the arterial diameter and Doppler sonographic images for blood flow analysis.

After these measurements, the cows received either the tocolytic drug isoxsuprine (200 mg/cow intravenously, Graeub Veterinary Products, Bern, Switzerland) or epidural anesthesia using 5 mL 2 % lidocaine (100 mg/cow injected into the sacrococcygeal space, Streuli Pharma Uznach, Switzerland). Location of the sacrococcygeal space was facilitated by up-and-down movements of the tail and the use of the hanging drop technique. B-mode and power-mode Doppler sonographic examinations were repeated after 30 min. One complete examination took 2 hours and was accompanied by collection of jugular blood into a heparinized blood tube (16 I.E. heparin/mL blood, Sarstedt, Nürnbrecht, Germany) for measurement of progesterone concentration.

1.3. Progesterone measurement

Blood was centrifuged at 4,000 rpm for 10 min and the plasma stored at -22°C. Progesterone was measured with the RIA kit IM1188 from Beckman Coulter GmbH (Krefeld, Germany) according to the producer's protocol. The intra- and interassay variation coefficients were 4.5 % and 8.5 %.

1.4. Data collection, analysis, and statistics

1.4.1. Blood flow measurement in the uterine arteries

The software program PixelFlux (Chameleon Software, Münster, Germany) was used to analyze ultrasound images and to determine vessel diameter (DM), pulse rate (PR), resistance index (RI), time-averaged mean velocity (TAMV) and blood flow volume (BFV). The diameter was measured in four B-mode images that showed a perfectly circular artery and no motion artifacts, and the mean was calculated from the four measurements. Pulse rate, RI, TAMV and BFV were calculated from Doppler sonographic images. For each artery, four images were selected that showed at least two representative and uniform Doppler waves. The mean was calculated from the four measurements. Pulse rate was defined as number of spectral waves per unit of time [min^{-1}]. The RI describes the resistance to flow distal to the point of measurement and is calculated using the formula RI=(D-S)/S, where D is the end-diastolic blood flow velocity and S the peak-systolic velocity. The TAMV of the arterial blood during a cardiac cycle is derived from the formula TAMV [cm/sec]=(TAMF x c)/(2F x cos α), where TAMF is the time-averaged maximum rate shift over the cardiac cycle, c is the ultrasound propagation velocity, F the transmitted wave rate and α the angle between the ultrasound beam and the blood flow direction [8]. The BFV was calculated using the formula BFV [cm^3/sec]=TAMV x A, where A is the arterial circumference, derived from the DM and using $A= \pi \times (DM/2)^2$.

1.4.2. Blood flow measurement in placentomes

The same software program (PixelFlux, Chameleon Software) was used for analysis of perfusion of placentomes. The transducer was positioned to image the maximum size of the placentomes. Slight adjustments in location of the transducer relative to the placentome were made to achieve a maximum number of color pixels in the placentome before freezing the images. The area of the placentome that appeared in color in the power-mode Doppler sonogram, representing the area with measurable blood flow (Fig. 1), as well as the entire area of the placentome, which was defined as region of interest, were traced and the areas measured. The colored area was expressed as a proportion of the entire region of interest, and the proportions calculated from the four measurements per placentome were averaged, generating the measure referred to as relative placentome perfusion (rPP), which was used for analysis [13].

In power-mode Doppler sonography, the amount of moving cells in the blood corresponds with the color of pixels, and therefore the RGB scale, included in all power Doppler sonograms (Fig. 1), was used to assess semiquantitatively the amount of moving cells per unit area (pixel). The RGB scale was divided into 143 color grades. Grade 1 corresponded to the color black and grade 143 corresponded to light yellow. Black pixels represent no movement and yellow pixels represent maximum amount of moving cells in the blood.

A software program was developed for quantification of blood flow. The RGB color values of all pixels in the region of interest were expressed as a ratio of all pixels and calculated as

$$\text{Colored pixels (Cp)} = \frac{\sum (x * pixel)}{\sum all\ pixels}$$

Where *x* is the color grade on the RGB scale and *pixel* is the number of pixels for one of the 143 color grades.

In a second step, the analysis was limited to pixels representing a high amount of blood flow. Pixels with color grades from orange to yellow (Cp84) corresponding to color grades 84 to 143 of the RGB scale were evaluated.

$$\text{Pixel orange (Cp 84)} = \frac{\sum (Cp84 \cdot pixel)}{\sum all\ pixels}$$

The calculated Cp and Cp84 values from the same four measurements per placentome used for rPP were averaged and used for further analyses.

1.4.3. Statistics

The calculated values were entered into an Excel file (Microsoft, Wallisellen, Switzerland) and the add-in statistic program StatEL (ad Science Company, Paris, France) was used for analysis of the sonographic variables. The program Stata (StataCorp, College Station, TX, USA) was used for the regression model and the multivariate regression. The Shapiro-Wilk test was used to test for normality. Normal data with homogeneity of variance (DM, TAMV, BFV) were analyzed using analysis of variance, and a post hoc test, i.e. Bonferroni, was used for comparison between different time points. The paired *t*-test was used for comparison of variables before and after treatment. Not normal distributed data (RI, HR, rPP, CP, Cp84) were analyzed using the Friedman and the Wilcoxon signed-rank test. The combined TAMV and BFV were calculated as mean values of measurements from the arteries of the pregnant and the non-pregnant horn. Results were expressed as mean ± standard deviation. A P-value ≤ 0.05 was considered significant. Correlations between progesterone concentrations, the age of the cows and all sonographic variables, as well as between the variables measured in the uterine arteries (RI, TAMV and BFV) and in the placentomes (rPP, CP) were calculated. Univariate linear regression models with the week prepartum as dependent variable and the sonographic parameter as well as the progesterone concentration as independent variables were calculated. The independent variables with a P < 0.2 were integrated into a multivariate regression model. Stepwise backward elimination regression was carried out. The final model consisted only variables with a P ≤ 0.01.

2. Results

2.1. Changes in uterine and placentome perfusion at the end of gestation

The changes in diameter of the ipsilateral ($P = 0.07$) and contralateral uterine arteries ($P = 0.08$) in the last month of gestation missed the significance level narrowly. The pulse rate in the uterine arteries increased from 75.78 ± 10.78 bpm at 4.5 weeks ap to 84.20 ± 9.85 bpm at 0.5 weeks ante partum (ap) ($P < 0.001$). The RI remained unchanged during the study period. The TAMV and the BFV (Fig. 2) in the arteries of the gravid and the non-gravid horn combined changed (TAMV $P < 0.05$, BFV $P < 0.01$). TAMV and BFV decreased in the ipsilateral uterine artery between 4.5 and 0.5 weeks ap by 10.8 % and 12.1 %, but remained unchanged in the contralateral uterine artery.

The rPP in both uterine horns did not change significantly during the study period. Similar to the rPP, the quotient Cp of the gravid and non-gravid horns combined missed the significance level narrowly (Fig. 2, $P = 0.09$). The placentome blood flow assessed by pixel grading in the yellow-to-orange color spectrum (Cp84) did not change significantly during the study period.

2.2. Correlations of sonographic variables

2.2.1. Age of the dam

Except RI and TAMV the sonographic variables showed a significant, but very weak correlation to the age of the dam (Table 1).

2.2.2. Correlation between sonographic variables

The RI showed a good correlation to TAMV ($TAMV = -254.3*RI + 250.5$; $r^2=0.38$; $P < 0.0001$). All other correlations were weak or not significant (Table 1).

2.2.3. Progesterone concentration

The progesterone concentration decreased in the last month of gestation ($P < 0.001$), but correlations with sonographic variables were weak or did not exist (r^2 ranged from 0.00005 to 0.3). The variables pulse rate, DM and BFV of the contralateral uterine artery remained in the model after backward elimination in stepwise regressions. In the multivariate regression analysis the highest correlation coefficient was calculated between BFV in the contralateral uterine artery, progesterone concentration and week ap ($r^2=0.4$; $P < 0.0001$).

2.3. Differences in blood flow between ipsilateral and contralateral uterine arteries

The DM of the ipsilateral and contralateral uterine arteries differed (14.90 ± 1.83 versus. 11.19 ± 1.69 mm, $P < 0.0001$, Fig. 3a). The RI was smaller (0.50 ± 0.06 versus 0.57 ± 0.06; Fig. 3b) and the TAMV (131.60 ± 22.23 cm/ sec versus 96.76 ± 23.50 cm/sec; Fig. 3c) and BFV (229.00 ± 54.69 cm^3/sec versus 99.83 ± 40.56 cm^3/sec; Fig. 3d) were larger in the ipsilateral uterine artery than in the contralateral uterine artery (all $P < 0.0001$).

The rPP was 12 % larger in the gravid horn than in the non-gravid horn ($P < 0.05$; Fig. 3e). Results for pixel color grading were similar; Cp was 21.1 % larger and Cp84 was 30.7 % larger in the gravid horn than in the non-gravid horn (both $P < 0.001$; Fig. 3f).

2.4. Effect of lidocaine and isoxsuprine on blood flow in the uterine arteries and placentomes

3.4.1. **Epidural anesthesia with lidocaine**

After epidural anesthesia with lidocaine, the DM of the ipsilateral uterine artery decreased from 14.79 ± 1.96 to 14.64 ± 1.89 mm ($P < 0.05$) and the pulse frequency of the ipsilateral artery decreased from 78.22 ± 10.72 to 76.62 ± 10.67 bpm ($P < 0.05$). The RI was not affected by the epidural anesthesia. The TAMV ($P < 0.05$; Fig. 4a) and the BFV ($P < 0.01$; Fig. 4b) increased by 5.4% and 7.9% in the contralateral but not the ipsilateral uterine artery. The BFV in both arteries combined were not affected by the epidural anesthesia. For both uterine horns together, epidural anesthesia caused an increase in rPP by 9.8 % ($P \leq 0.05$; Fig. 5a). An increase in the gravid horn (10.1 %, $P \leq 0.05$; Fig. 5a) but not in the non-gravid horn.

The effect on the color pixel grading (Cp) was similar; there was an increased in both horns combined of 12.4 % ($P < 0.01$; Fig. 5b), an increase in the gravid horn of 11.5% ($P \leq 0.05$; Fig. 5b) and a trend toward significance in the non-pregnant horn ($P = 0.08$). The results for Cp84 were analogous (Fig. 5c).

3.4.2. **Uterine relaxant isoxsuprine**

After intravenous administration of isoxsuprine, the DM of the ipsilateral and contralateral uterine arteries increased by 4.7 % from 15.01 ± 1.73 mm to 15.72 ± 1.86 mm and by 10.8 % from 11.34 ± 1.61 to 12.57 ± 1.81 mm (both $P < 0.00001$; Fig. 6a) and the pulse rate by 49.3 % from 78.63 ± 11.60 bpm to 117.4 ± 16.11 bpm, respectively (both $P < 0.00001$). The RI decreased in the ipsilateral uterine artery by 24.2 % and in the contralateral uterine artery by 14.9 % (ipsilateral from 0.50 ± 0.06 to 0.38 ± 0.04, contralateral from 0.57 ± 0.06 to 0.48 ± 0.07; both $P < 0.00001$; Fig. 6b). The TAMV increased in the ipsilateral uterine artery by 7.1 % (130.09 ± 20.82 cm/sec to 139.29 ± 24.65 cm/sec, $P < 0.05$) but not in the contralateral uterine artery

(Fig. 6c). The BFV increased from 230.34 ± 54.28 cm^3/sec to 269.33 ± 61.80 cm^3/sec (16.9 %) in the ipsilateral artery and from 103.87 ± 40.51 cm^3/sec to 127.58 ± 53.45 cm^3/sec (22.8 %) in the contralateral uterine artery (both P < 0.00001; Fig. 6d). The combined BFV of both arteries increased from 167.10 ± 79.48 cm^3/sec to 198.45 ± 91.57 cm^3/sec (18.8 %; P < 0.00001).

The rPP increased by 18.1% in the gravid horn (P < 0.01), by 10.2% in the non-gravid horn (P < 0.05) and by 13 % in both horns combined (P < 0.01; Fig. 7a). Color pixel grading (Cp) for both horns combined increased by 19.1 % (P < 0.001). There was an 18% increase in the gravid horn (P < 0.01) and a 24.2 % increase in the non-gravid horn (P < 0.01; Fig. 7b). Color pixel grading (Cp84) increased in the placentomes in the non-gravid horn by 42 % (P < 0.05) and in the gravid horn by 22.3 % (P < 0.01), which led to increase for both horns combined by 50.4 % (Fig. 7c, P < 0.01).

3. Discussion

The increased demand for nutrients and oxygen by the uterus and growing fetus is accompanied by an increase in uterine blood flow [14]. Monthly Doppler sonographic examination of the uterine arteries in lactating Holstein cows showed a linear increase in uterine blood flow in the second part of gestation [15]. From day 30 to day 270 of gestation, the TAMV increased three-fold, the DM of the uterine arteries 20-fold and the BFV 17-fold [8].

In contrast, these variables changed little during the last few weeks of gestation in the present study. The most pronounced change was an 11 % increase in pulse rate, which was similar to a 7.6 % increase reported recently [9]. The increase in pulse rate in pregnant women is attributed to an increase in plasma volume and is most pronounced in the second half of gestation [16]. In women, the increase in plasma volume is accompanied by a reduction in RI, which allows more blood to be transported to the placenta. This is achieved through structural widening of the uterine vascular bed and reduction in vascular tone [17]. A continuously decreasing RI also occurred in cows during the first 36 weeks of gestation [8]. The RI of the ipsilateral uterine artery did not change in the present study, which was in agreement with a study involving monthly examinations of pregnant cows [4], but was in contrast to a recent report that the RI 1 week ap was lower than the value recorded 5 weeks ap [9]. These discrepancies are difficult to explain because the factors affecting the RI in cattle remain unclear. Likewise, the differences in TAMV and BFV between 4.5 or 4 weeks and 0.5 week ap contradict the results of other studies; these two variables decreased by 10.8 and 12.1 %, respectively, but did not change during the same time in other studies [9, 15]. A slight decrease in BFV occurred in the last month of gestation in another study [8]. Cardiac output diminishes during the last 8 weeks of pregnancy in women for unknown reasons, which could explain, at least in part, a decrease in BFV [16].

Similar changes were also seen with the color pixel grading Cp. There was a parallel between blood flow measured in the uterine arteries and in the placentomes. This was also detectable in the correlations between the uterine and some placentome variables, although the correlations were weak. The physiologic control of the uterine blood supply could not be clarified in the present study. It is possible that hormonal mechanisms are indirectly responsible for an increase in uterine and placentome blood flow by increasing cardiac output and uterine blood flow [16]. Estrogen and progesterone also have an effect on uterine perfusion. Studies in sheep and pigs have shown that in the follicular phase, which is characterized by an increasing estrogen-to-progesterone ratio, the uterine blood flow increases, and that in the luteal phase, characterized by high progesterone and low estrogen concentrations, the uterine blood flow decreases [18, 19]. Similar studies in cattle have not been conclusive. A positive correlation between uterine perfusion and blood levels of estrogen and a negative correlation between uterine perfusion and blood levels of progesterone were determined in two studies [3, 20], whereas in cycling cows, the greatest blood flow was measured after the decline in progesterone but one day before the day of maximum estrogen concentration [5]. Most blood flow variables in the present study were not or only minimally correlated with the progesterone concentration, but over the entire study period, there was a correlation between the increase in BFV in the contralateral uterine artery and the decrease in progesterone concentration. The effect of sex steroids on blood flow could be based on different mechanisms because BFV is affected by multiple factors including vessel DM, RI and TAMV [5]. For instance, estrogens have an indirect effect on blood flow through stimulation of endothelial NO synthesis [21, 22], or they can have a direct vasodilatory effect by lowering calcium uptake by the vascular smooth muscle in the uterine arteries [23]. An effect of progesterone on the contractility of the uterine artery was shown in pigs [24]. The contractility of the uterine arteries of gilts decreased after ovariectomy in the luteal phase [23].

In this study, the RI of the ipsilateral uterine artery was smaller and the DM, TAMV and the BFV greater compared with the contralateral artery, which was in agreement with other studies [4, 8]. It is apparent from those studies that the differences between the two arteries increase from the second trimester because the decrease in RI and the increase in the other variables are considerably steeper in the ipsilateral than in the contralateral artery [4, 8]. The difference in blood flow variables of the uterine arteries is mirrored by the rPP and color pixel grading; higher values of the latter in the gravid horn indicate that increased uterine perfusion is accompanied by increased perfusion of the placentomes. This shows that power-mode Doppler sonography allows meaningful measurement of placentome perfusion based on the measurement of the amount of blood cells per unit area. Furthermore, changes in blood flow variables of the uterine arteries appear to have a direct effect on placentome perfusion, which suggests that placentome perfusion can be estimated using blood flow in the uterine arteries.

Drugs that are often used in bovine obstetrics may affect the perfusion of the uterine and umbilical arteries [9]. Epidural anesthesia with 2% lidocaine is commonly used in cows to suppress the Ferguson reflex during treatment of dystocia, and also is used in protracted labor in women to improve oxygenation of the fetus [12]. Uterine perfusion of cows is affected by epidural anesthesia in several ways [9]. The pulse rate of the contralateral uterine artery, but not the ipsilateral artery, was reduced after epidural anesthesia, but this difference was thought to be due to the successive rather than concurrent measuring protocol. In the present study, a decrease in pulse rate was observed only in the ipsilateral uterine artery. Epidural anesthesia most likely reduces stress caused by the examination, which in turn results in a lower pulse rate [9].

In contrast to a recent study from our clinic [9], we only detected an increase in TAMV and BFV in the contralateral but not ipsilateral uterine artery; the reason for this is not clear. The BFV of the contralateral uterine artery is considerably smaller and therefore the unilateral increase did not translate into an overall increase in uterine BFV. Sample sizes were relatively small in both studies and it is therefore possible that large individual variation, which is common in cycling cows [5], was responsible for the discrepancy.

In agreement with another study [9], epidural anesthesia did not affect the RI. Studies in human obstetrics generated inconsistent results concerning the effect of epidural anesthesia on RI but most did not show an effect [25-29]. Despite the unchanged RI, the rPP and measurements of color pixel grading Cp and Cp84 increased significantly in the gravid horn, whereas in the non-gravid horn, there was a smaller increase with a trend toward significance albeit accompanied by increased TAMV and BFV. This may reflect a weakness of the study because only one placentome was examined in the non-gravid horn. Because the BFV did not increase in the ipsilateral uterine artery, presumably because of the decreasing pulse rate and the smaller DM compared to the pre-treatment values, a reduction in vascular resistance in the placentomes is a reasonable explanation for the measured increase in perfusion. However, the RI, defined to reflect this reduction, is an unreliable measure [25]; in the case of proportional unidirectional changes in end-diastolic blood flow velocity and peak systolic velocity, which are used to calculate the RI, this variable does not indicate a change.

Isoxsuprine is a β sympathomimetic drug and binds to β_2 receptors, which are abundant in the myometrium at the time of parturition, causing relaxation of the smooth musculature [30, 31]. It also has positive chronotropic and inotropic effects and causes peripheral vasodilation [30]. There was an increase in the pulse rate by 50 %, which was similar to the effect seen in another study [9], and we suspected that the increase in BFV by 19 % was due, at least in part, to the inotropic properties of isoxsuprine. Unlike an earlier study, in which the increase in BFV was limited to the contralateral uterine artery [9], we observed an increase in both arteries, albeit larger in the contralateral artery. This could have been due to the vasodilatory effect of isoxsuprine; the DM of the ipsilateral and contralateral uterine arteries increased by 5 % and 11 %, respectively. The unilateral increase in BFV in the contralateral artery in the former study also was accompanied by unilateral increase in DM in that vessel [9]. Individual variations related to vascular fibrosis from previous pregnancies have been described in cycling cows and could explain these differences [5]. The cows used in our study varied considerably in the number of previous pregnancies and with increasing age the blood flow in the placentomes decreased. However, RI and TAMV in the uterine arteries did not show any correlation to the age of the cows and BFV even increased with increasing age. The TAMV did not increase in the contralateral uterine artery as would have been expected based on the positive inotropic effect of isoxsuprine. This finding was similar to the results of another study, in which there even was a decrease in TAMV of the contralateral uterine artery [9]. According to the continuity equation, the decrease in TAMV can be explained by the larger increase in DM in the contralateral artery.

The decrease in RI by 24 % in the ipsilateral uterine artery and by 15 % in the contralateral uterine artery also can be attributed to the vasodilatory effect of isoxsuprine because the RI reflects the vascular resistance distal to the point of measurement. These results agree with previously published reductions in RI by 20 % and 11 %, respectively [8]. Similar findings were reported in pregnant women [32, 33].

An increase in placental perfusion after the administration of isoxsuprine in cows has been suspected based on the increase in BFV and reduction in RI in the uterine arteries [9,12]. This could be confirmed in the present study because direct measurement showed an increase in the perfused area of the placentomes in the gravid and non-gravid uterine horns. Thus, isoxsuprine has a direct positive effect on placental perfusion. So-called intrauterine resuscitative measures are used in human medicine to combat fetal hypoxia and improve fetal oxygen supply [12]. One such measure is the use of uterine relaxant drugs to reduce excessive uterine contractions and to improve uterine perfusion. In cows, it is also known that uterine contractions are accompanied by a lowered blood supply to the fetus [34], and it is therefore plausible that isoxsuprine given during dystocia improves placental perfusion through the elimination of contractions as well as its direct effect on perfusion of placentomes. This could be advantageous in delayed birth, for instance when a cow is prepared for Caesarean section [12]. However, isoxsuprine also has positive chronotropic and inotropic effects in the fetus [9], which could increase fetal oxygen consumption and further compromise an already hypoxic fetus. Epidural anesthesia might be preferable in these situations; although there was no improvement in uterine perfusion in contrast to an earlier study [9], perfusion of placentomes was nevertheless increased. This means that the advantages provided by isoxsuprine could also be achieved with epidural anesthesia without the risk of increasing fetal heart rate [9]. When the discussed limitations are taken into account, isoxsuprine as well as epidural anesthesia seem suitable for improving placental perfusion in cows in advanced pregnancy. This conclusion is based on results from a novel approach of direct assessment of placental perfusion. The determination of the rPP and the amount of moving cells in the blood (Cp) were useful for the direct assessment of placental perfusion. The selective measurement of the relative area with a very large amount of moving cells in the blood (Cp 84) did not appear to provide an advantage for assessing placental perfusion. The direct measurement of placental perfusion using power-mode sonography makes it possible to assess the effects of pharmacological measures to improve fetal well-being during parturition.

Acknowledgements

We thank Marco Hutter, ETH Zürich, Institute of Robotics and Intelligent Systems for developing the software for quantitation of blood flow in placentomes and Dr. med. vet. Penelope A. Baloi, Resident ECVDI, Division of Diagnostic Imaging, Vetsuisse Faculty, University of Zurich, for technical support.

References

[1] Ferrell CL, Ford SP. Blood flow steroid secretion and nutrient uptake of the gravid bovine uterus. J of Anim Sci. 1980;50:1113-21.

[2] Ford SP, Chenault JR. Blood flow to the corpus luteum-bearing ovary and ipsilateral uterine horn of cows during the oestrous cycle and early pregnancy. J Reprod Fertil. 1981;62:555-62.

[3] Waite LR, Ford SP, Young DF, Conley AJ. Use of ultrasonic Doppler waveforms to estimate changes in uterine artery blood flow and vessel compliance. J Anim Sci. 1990;68:2450-8.

[4] Bollwein H, Baumgartner U, Stolla R. Transrectal Doppler sonography of uterine blood flow in cows during pregnancy. Theriogenology. 2002;57:2053-61.

[5] Bollwein H, Meyer HH, Maierl J, Weber F, Baumgartner U, Stolla R. Transrectal Doppler sonography of uterine blood flow. Theriogenology. 2000;53:1541-52.

[6] Bollwein H, Maierl J, Mayer R, Stolla R. Transrectal color Doppler sonography of the A. uterina in cyclic mares. Theriogenology. 1998;49:1483-8.

[7] Dzięcioł M, Stańczyk E, Noszczyk-Nowak A, Michlik K, Kozdrowski R, Niżański W, et al. The influence of Sildenafil citrate on uterine tissue perfusion and the cardiovascular system during the luteal phase of the ovarian cycle in cows. Acta Histochemica. 2014;116:377-81.

[8] Panarace M, Garnil C, Marfil M, Jauregui G, Lagioia J, Luther E, et al. Transrectal Doppler sonography for evaluation of uterine blood flow throughout pregnancy in 13 cows. Theriogenology. 2006;66:2113-9.

[9] Waldvogel D, Bleul U. Effect of xylazine, isoxsuprine, and lidocaine on Doppler sonographic uterine and umbilical blood flow measurements in cows during the last month of pregnancy. Theriogenology. 2014;81:993-1003.
[10] Bleul U, Lejeune B, Schwantag S, Kahn W. Ultrasonic transit-time measurement of blood flow in the umbilical arteries and veins in the bovine fetus during stage II of labor. Theriogenology. 2007;67:1123-33.
[11] Bude RO, Rubin JM. Power Doppler sonography. Radiology. 1996;200:21-3.
[12] Garite TJ, Simpson KR. Intrauterine resuscitation during labor. Clin Obstet Gynecol. 2011;54:28-39.
[13] Luttgenau J, Beindorff N, Ulbrich SE, Kastelic JP, Bollwein H. Low plasma progesterone concentrations are accompanied by reduced luteal blood flow and increased size of the dominant follicle in dairy cows. Theriogenology. 2011;76:12-22.
[14] Satterfield MC, Bazer FW, Spencer TE, Wu G. Sildenafil Citrate Treatment Enhances Amino Acid Availability in the Conceptus and Fetal Growth in an Ovine Model of Intrauterine Growth Restriction. The Journal of Nutrition. 2010;140:251-8.
[15] Herzog K, Koerte J, Flachowsky G, Bollwein H. Variability of uterine blood flow in lactating cows during the second half of gestation. Theriogenology. 2011;75:1688-94.
[16] Hall Ga. Textbook of Medical Physiology (11 ed). Philadelphia: Saunders; 2005. p. 1034.
[17] Thornburg KL, Jacobson SL, Giraud GD, Morton MJ. Hemodynamic changes in pregnancy. Semin Perinatol. 2000;24:11-4.
[18] Ford SP. Control of uterine and ovarian blood flow throughout the estrous cycle and pregnancy of ewes, sows and cows. J Anim Sci. 1982;55 Suppl 2:32-42.
[19] Rupnow HL, Phernetton TM, Shaw CE, Modrick ML, Bird IM, Magness RR. Endothelial vasodilator production by uterine and systemic arteries. VII. Estrogen and progesterone effects on eNOS. Am J Physiol-Heart C. 2001;280:H1699-705.
[20] Ford SP, Chenault JR, Echternkamp SE. Uterine blood flow of cows during the oestrous cycle and early pregnancy: effect of the conceptus on the uterine blood supply. J Reprod Fertil. 1979;56:53-62.
[21] Magness RR, Rosenfeld CR. Local and systemic estradiol-17 beta: effects on uterine and systemic vasodilation. Am J Physiol. 1989;256:E536-42.
[22] Kim KH, Bender JR. Rapid, estrogen receptor-mediated signaling: why is the endothelium so special? Science Signaling. 2005:pe28.
[23] Stice SL, Ford SP, Rosazza JP, Van Orden DE. Role of 4-hydroxylated estradiol in reducing Ca2+ uptake of uterine arterial smooth muscle cells through potential-sensitive channels. Biol Reprod. 1987;36:361-8.

[24] Ford SP, Reynolds LP, Farley DB, Bhatnagar RK, Van Orden DE. Interaction of ovarian steroids and periarterial alpha 1-adrenergic receptors in altering uterine blood flow during the estrous cycle of gilts. Am J Obstet Gynecol. 1984;150:480-4.
[25] Valentin M, Ducarme G, Ceccaldi PF, Bougeois B, Luton D. Uterine artery, umbilical, and fetal cerebral Doppler velocities after epidural analgesia during labor. Int J Gynecol Obstet. 2012;118:145-8.
[26] Hughes AB, Devoe LD, Wakefield ML, Metheny WP. The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal term labor. Obstet Gynecol. 1990;75:809-12.
[27] Patton DE, Lee W, Miller J, Jones M. Maternal, uteroplacental, and fetoplacental hemodynamic and Doppler velocimetric changes during epidural anesthesia in normal labor. Obstet Gynecol. 1991;77:17-9.
[28] Alahuhta S, Rasanen J, Jouppila P, Jouppila R, Hollmen AI. Epidural sufentanil and bupivacaine for labor analgesia and Doppler velocimetry of the umbilical and uterine arteries. Anesthesiology. 1993;78:231-6.
[29] Ramos-Santos E, Devoe LD, Wakefield ML, Sherline DM, Metheny WP. The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal and hypertensive patients during active term labor. Obstet Gynecol. 1991;77:20-6.
[30] Plumb D. Veterinary drug handbook. Pharma Vet Publishing; White Bear Lake. 1999. 113-4.
[31] Windholz M. Budavari S BR, Otterbein E. The Merck Index. Merck, Rahway, NJ. 1983. 2194.
[32] Deutinger J, Rudelstorfer R, Pattermann A, Bernaschek G. Vaginosonographic velocimetry in uterine arteries before and after administration of beta-mimetics. Brit J Obstet Gynaecol. 1992;99:417-21.
[33] Wright JW, Patterson RM, Ridgway LE, 3rd, Berkus MD. Effect of tocolytic agents on fetal umbilical velocimetry. Am J Obstet Gynecol. 1990;163:748-50.
[34] Bleul U, Schwantag S, Kahn W. Blood gas analysis of bovine fetal capillary blood during stage II labor. Theriogenology. 2008;69:245-51.

Table 1

	age	RI	TAMV	BFV
BFV	BFV = 4.594*age + 120.2 r^2=0.052; $P < 0.01$	BFV = -304.6*RI + 327.8 r^2=0.069; $P < 0.01$	BFV = 0.5298*TAMV + 103.9 r^2=0.036; $P < 0.001$	
rPP	rPP = -0.2599*age + 14.11 r^2=0.061; $P < 0.01$	rPP = -12.21*RI + 18.15 r^2=0.04; $P < 0.05$	rPP = 0.0437*TAMV + 6.617 r^2=0.088; $P < 0.001$	n. s.
CP	Cp = -0.0006729*age + 0.02072 r^2=0.067; $P < 0.01$	n. s.	Cp = 0.0000833*TAMV + 0.004727 r^2=0.088; $P < 0.001$	n. s.

Fig. 1

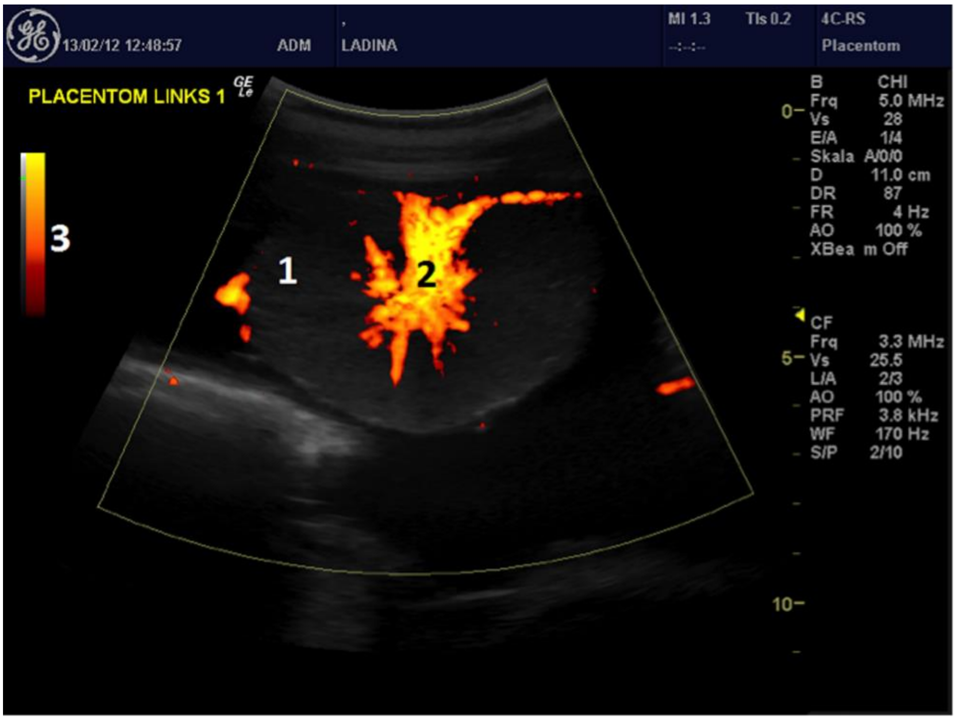
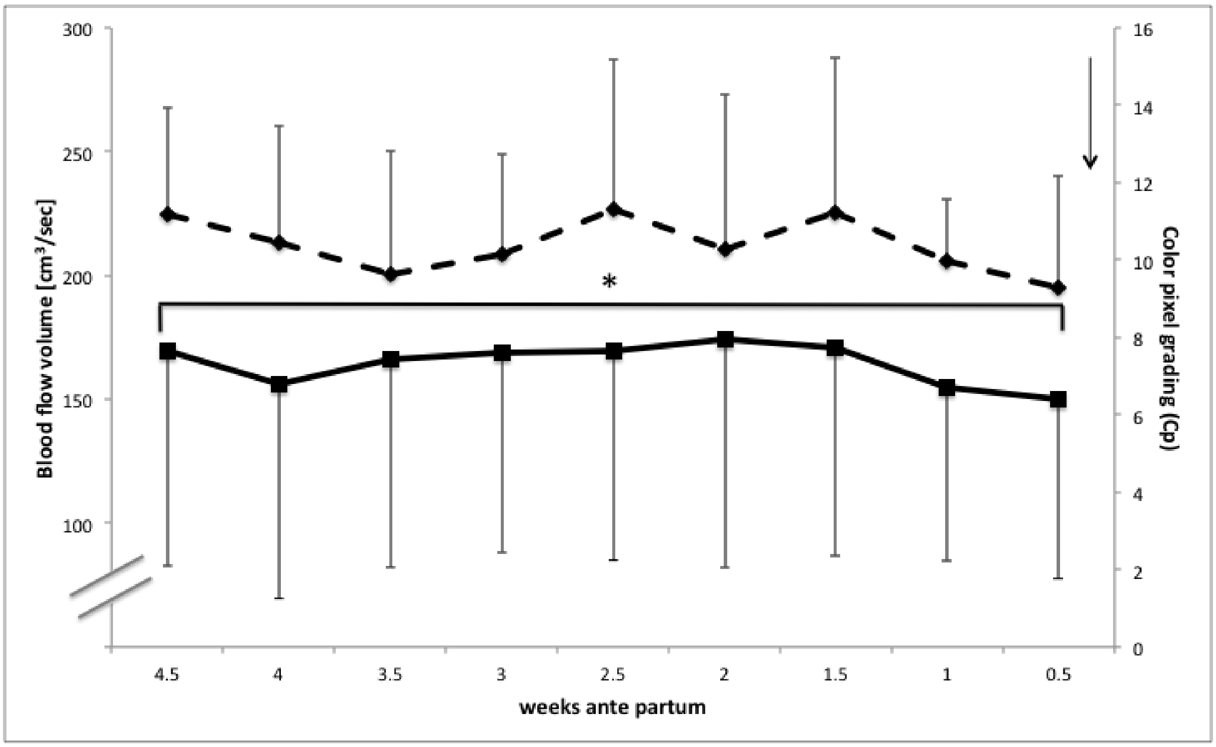
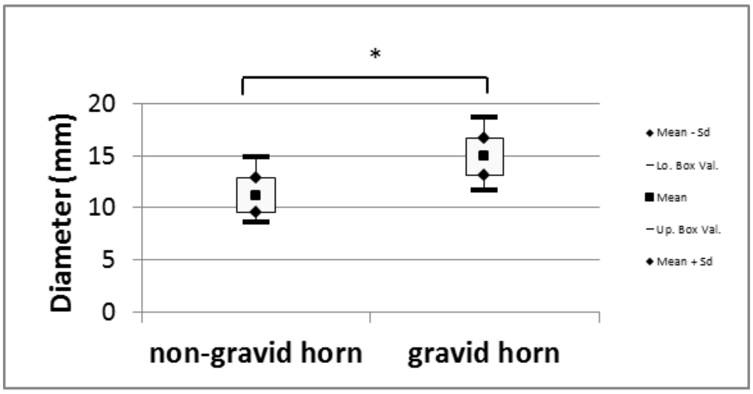

13/02/12 12:48:57
ADM
LADINA
MI 1.3
TIs 0.2
4C-RS
Placentom
PLACENTOM LINKS 1
1
2
3
B CHI
Frq 5.0 MHz
Vs 28
E/A 1/4
Skala A/0/0
D 11.0 cm
DR 87
FR 4 Hz
AO 100 %
XBea m Off
CF
Frq 3.3 MHz
Vs 25.5
L/A 2/3
AO 100 %
PRF 3.8 kHz
WF 170 Hz
S/P 2/10
0
5
10

Fig. 2

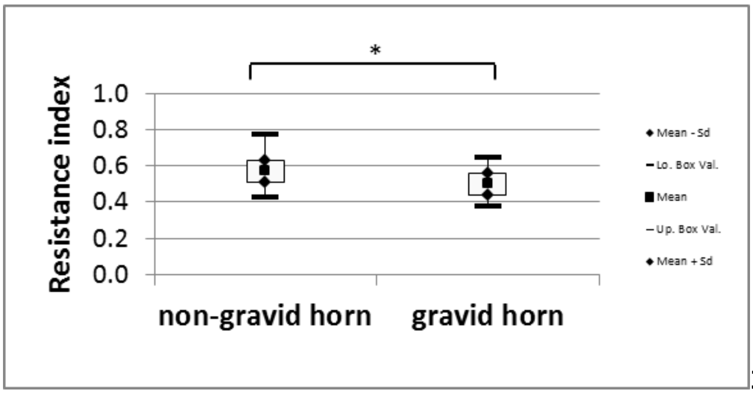


300
250
200
150
100
16
14
12
10
8
6
4
2
0
Blood flow volume [cm³/sec]
Color pixel grading (Cp)
*
4.5
4
3.5
3
2.5
2
1.5
1
0.5
weeks ante partum

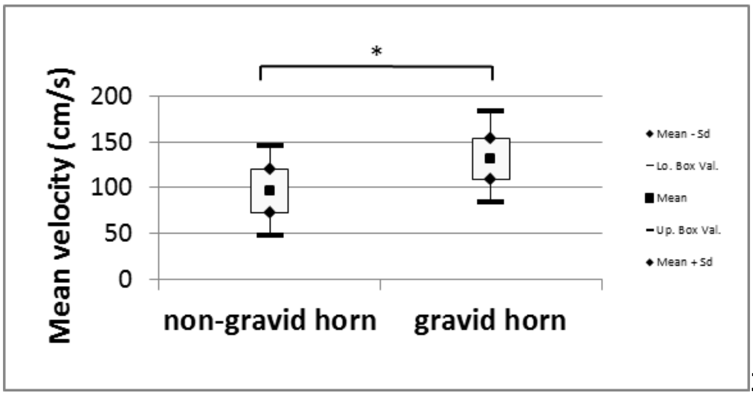
Fig. 3



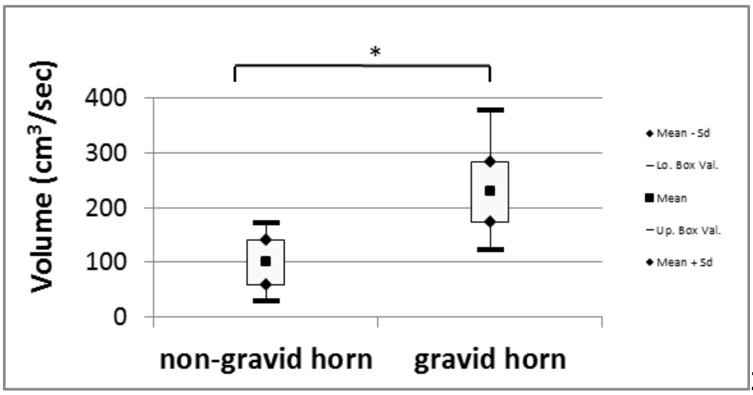
3a



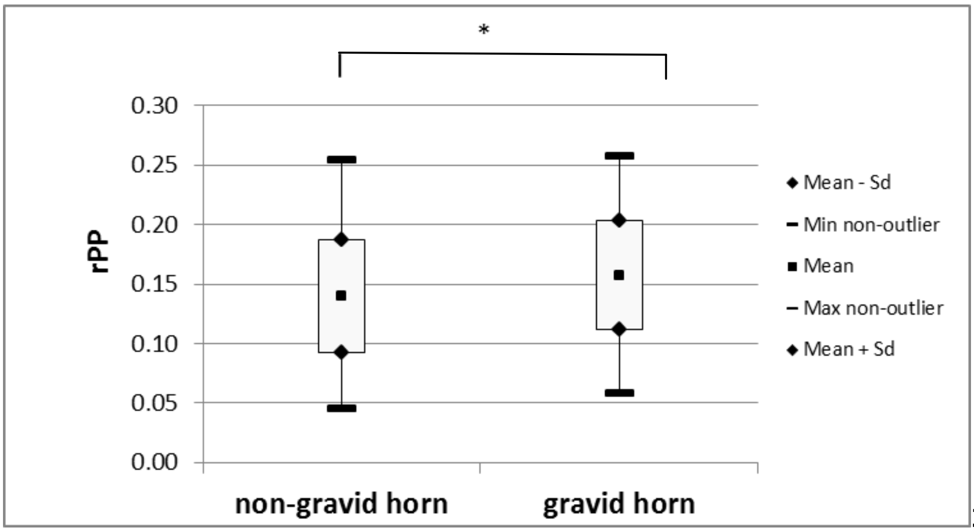
3b



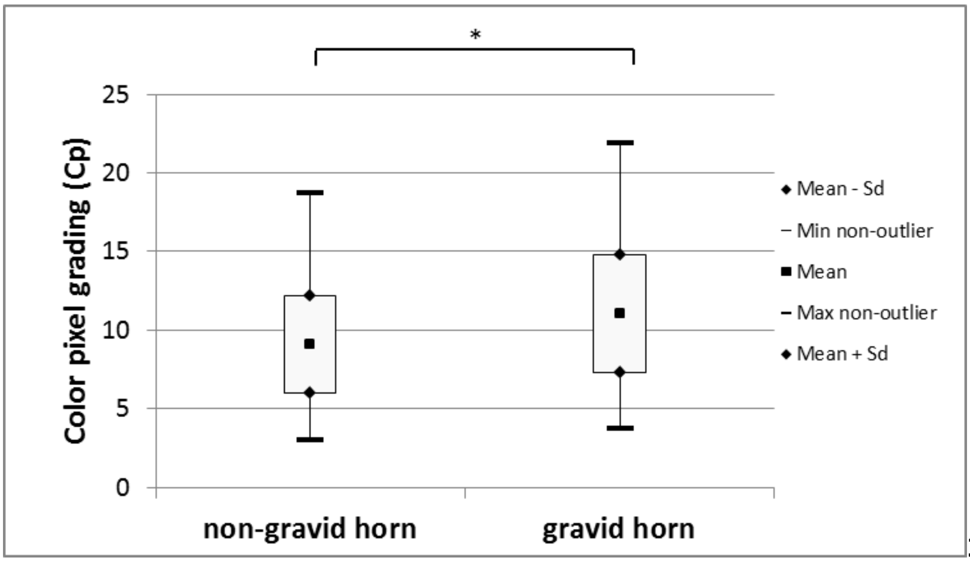
3c



3d

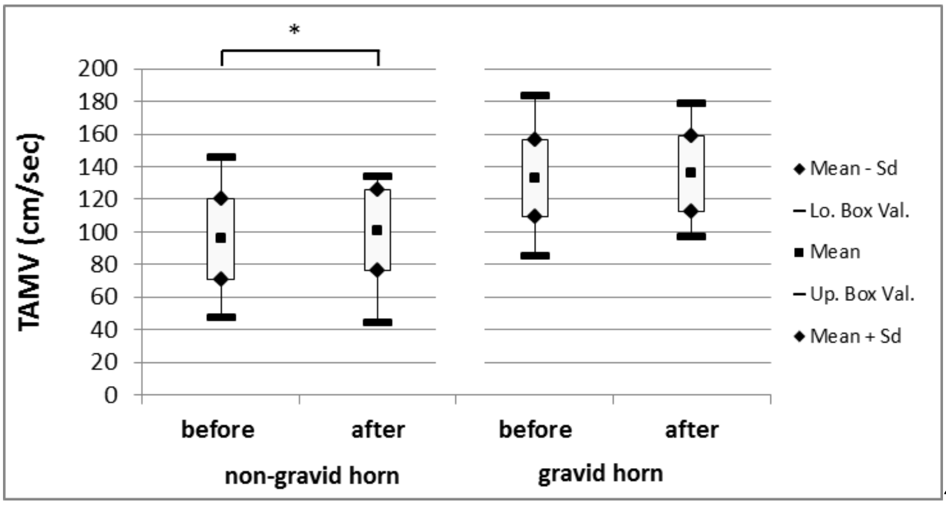

*
0.30
0.25
0.20
0.15
0.10
0.05
0.00
rPP
non-gravid horn
gravid horn
Mean - Sd
Min non-outlier
Mean
Max non-outlier
Mean + Sd

3e

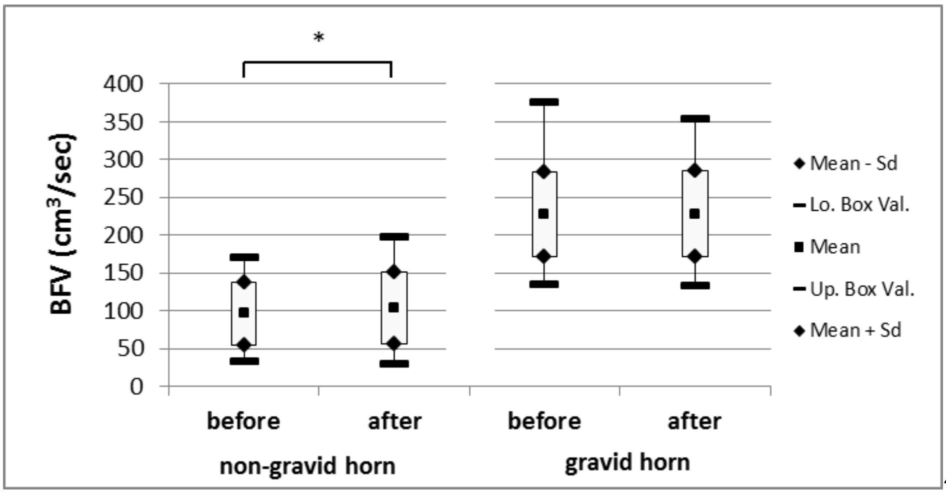

*
25
20
15
10
5
0
Color pixel grading (Cp)
non-gravid horn
gravid horn
Mean - Sd
Min non-outlier
Mean
Max non-outlier
Mean + Sd

3f

Fig. 4

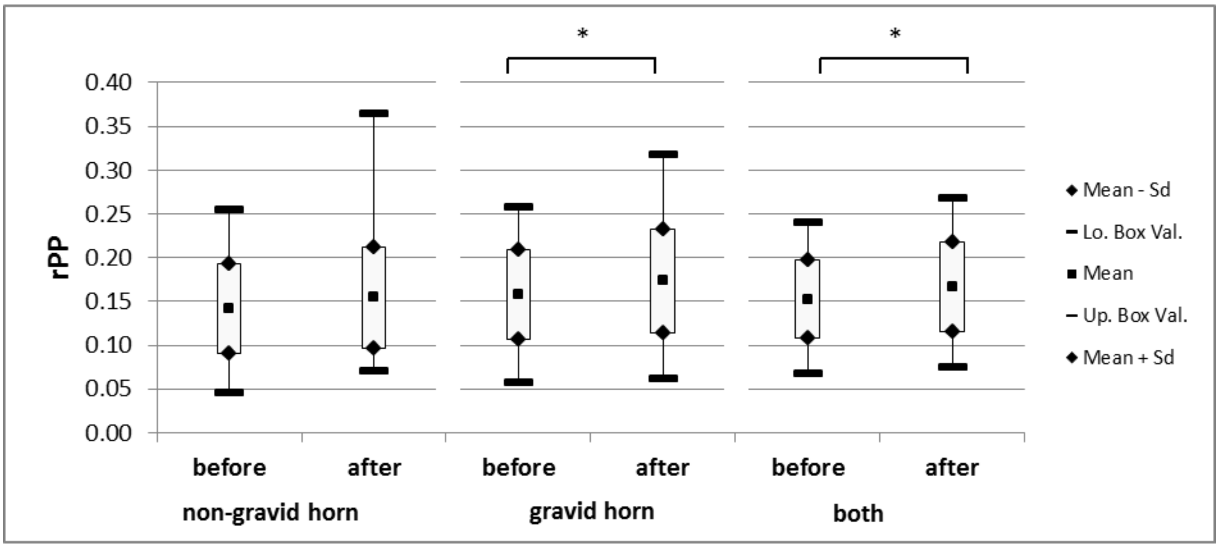

*
200
180
160
140
120
100
80
60
40
20
0
TAMV (cm/sec)
before
after
before
after
non-gravid horn
gravid horn
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

4a


*
400
350
300
250
200
150
100
50
0
BFV (cm^3/sec)
before
after
before
after
non-gravid horn
gravid horn
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

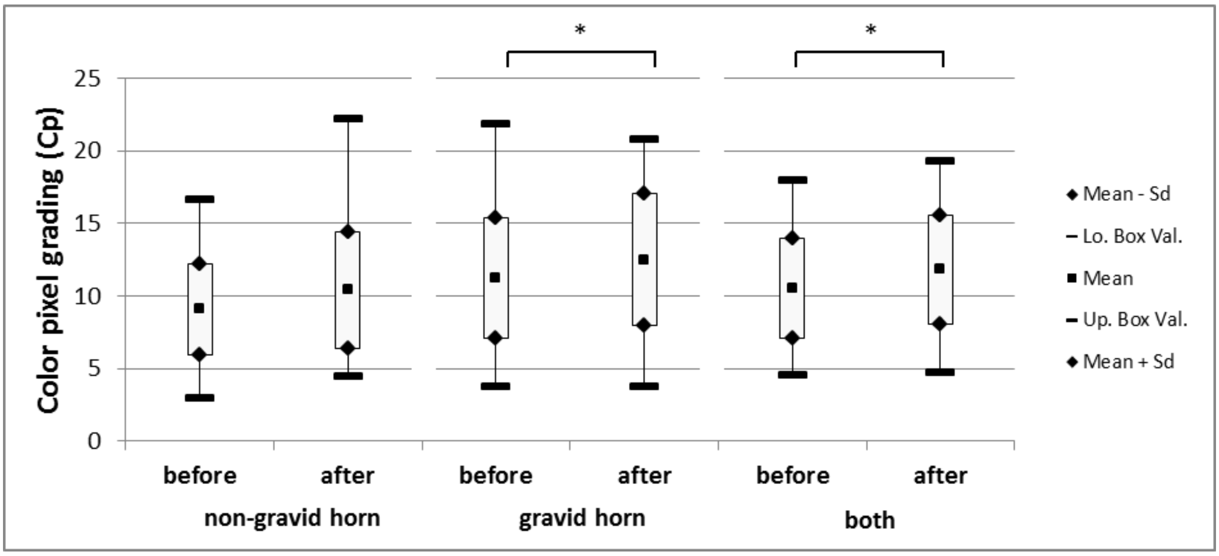
4b

Fig. 5



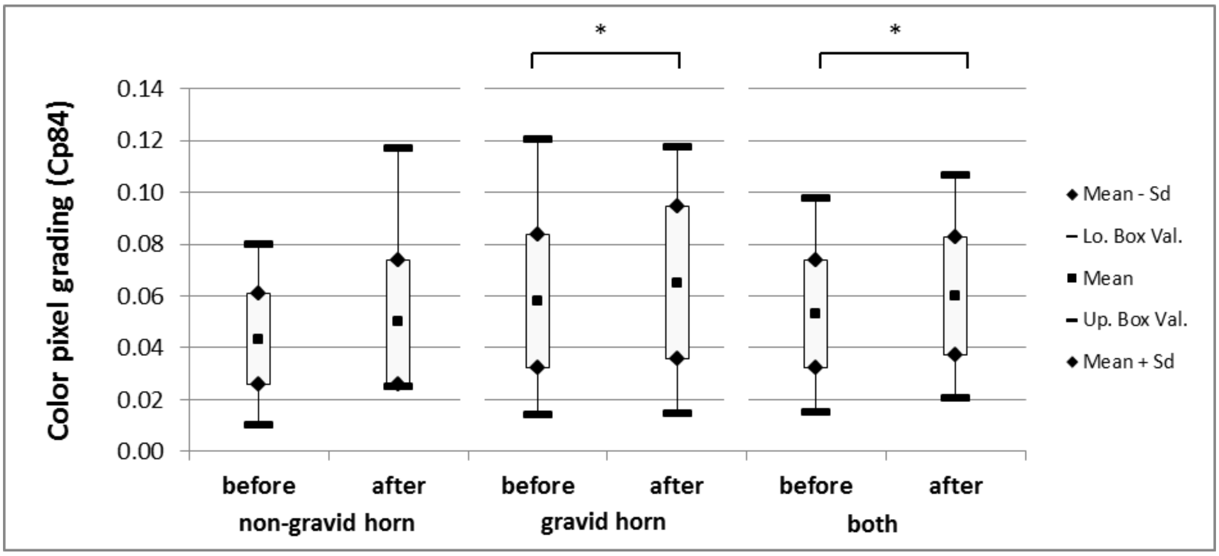
*
*
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
rPP
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd
before
after
before
after
before
after
non-gravid horn
gravid horn
both

5a



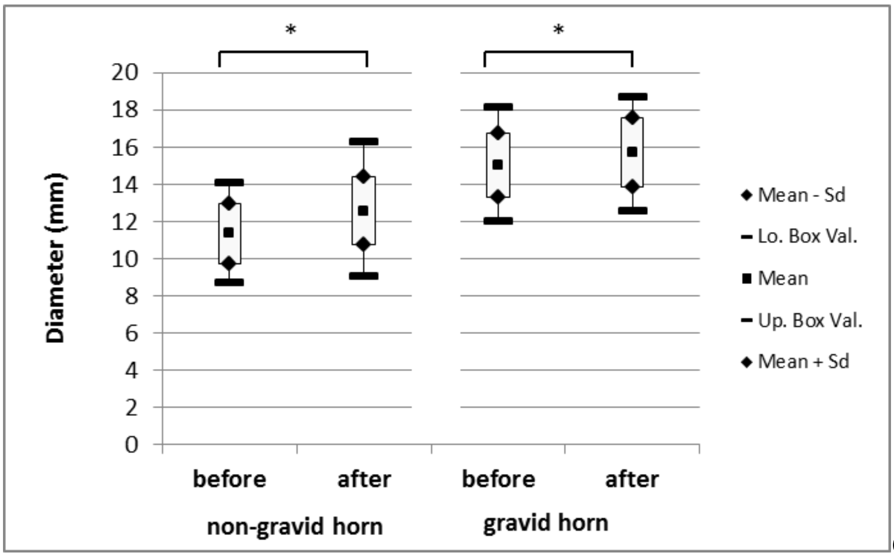
*
*
25
20
15
10
5
0
Color pixel grading (Cp)
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd
before
after
before
after
before
after
non-gravid horn
gravid horn
both

5b

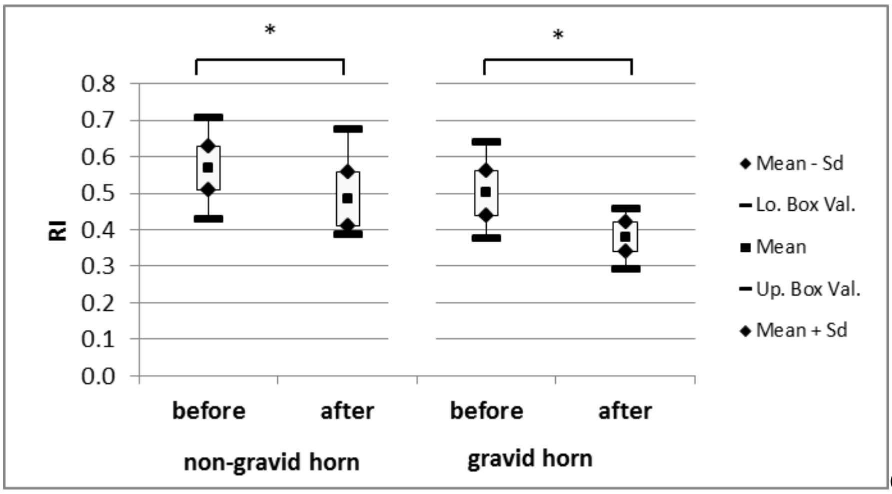

*
*
Color pixel grading (Cp84)
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
before
after
before
after
before
after
non-gravid horn
gravid horn
both
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

5c

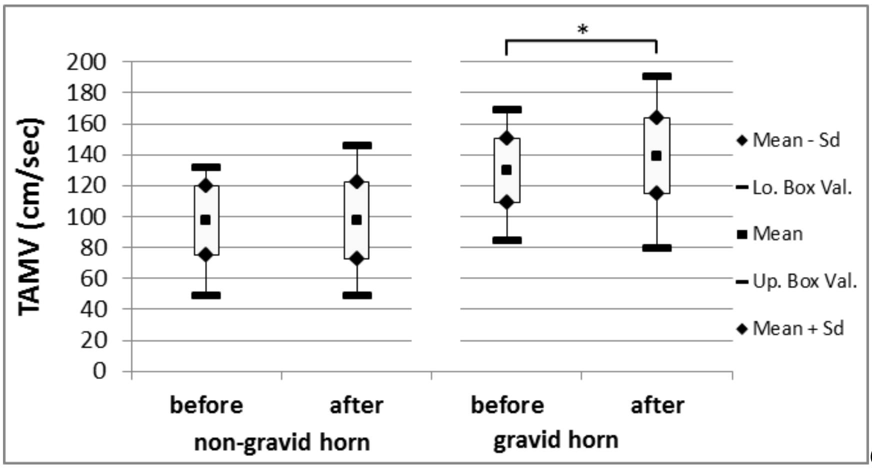
Fig. 6


*
*
Diameter (mm)
20
18
16
14
12
10
8
6
4
2
0
before
after
before
after
non-gravid horn
gravid horn
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

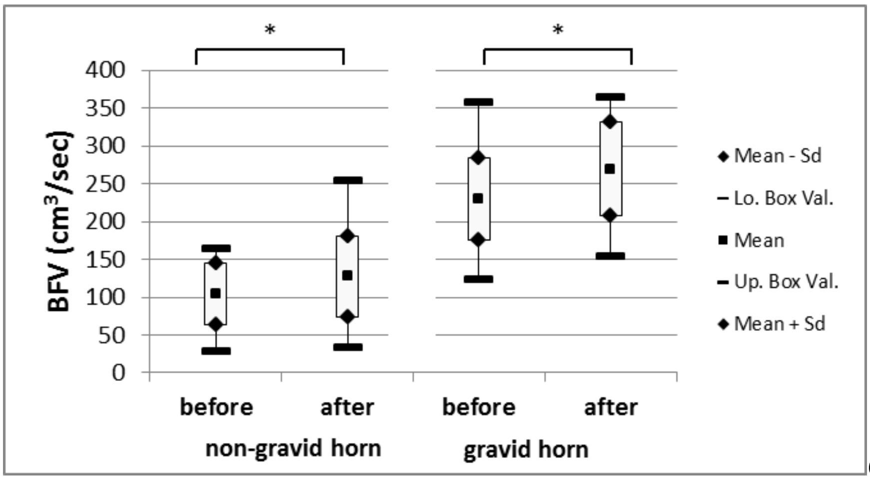
6a


*
*
RI
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
before
after
before
after
non-gravid horn
gravid horn
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

6b

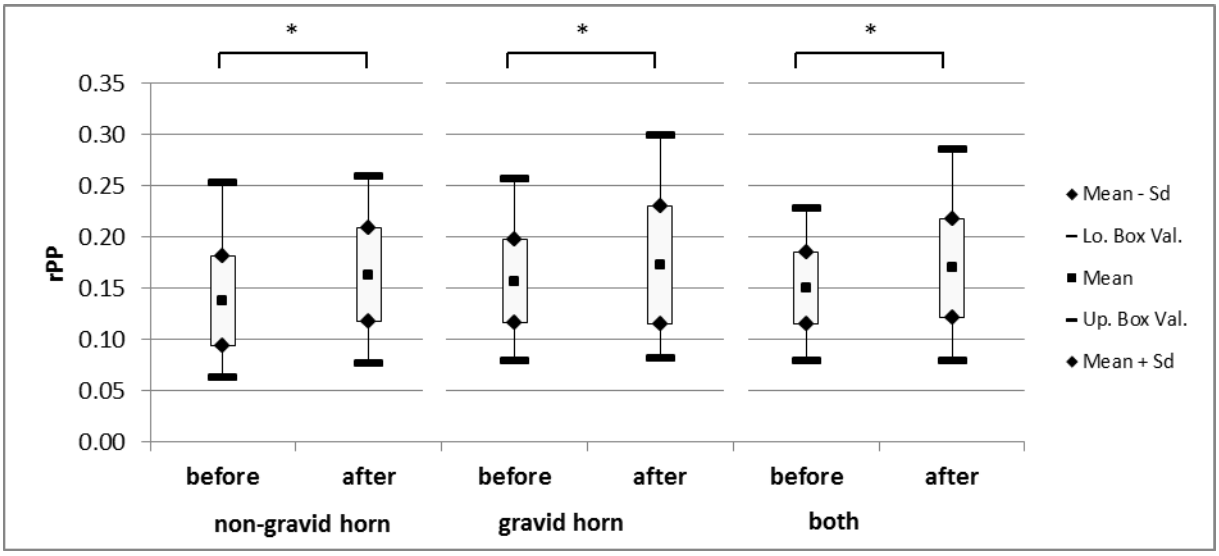

*
200
180
160
140
120
100
80
60
40
20
0
TAMV (cm/sec)
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd
before
after
before
after
non-gravid horn
gravid horn

6c

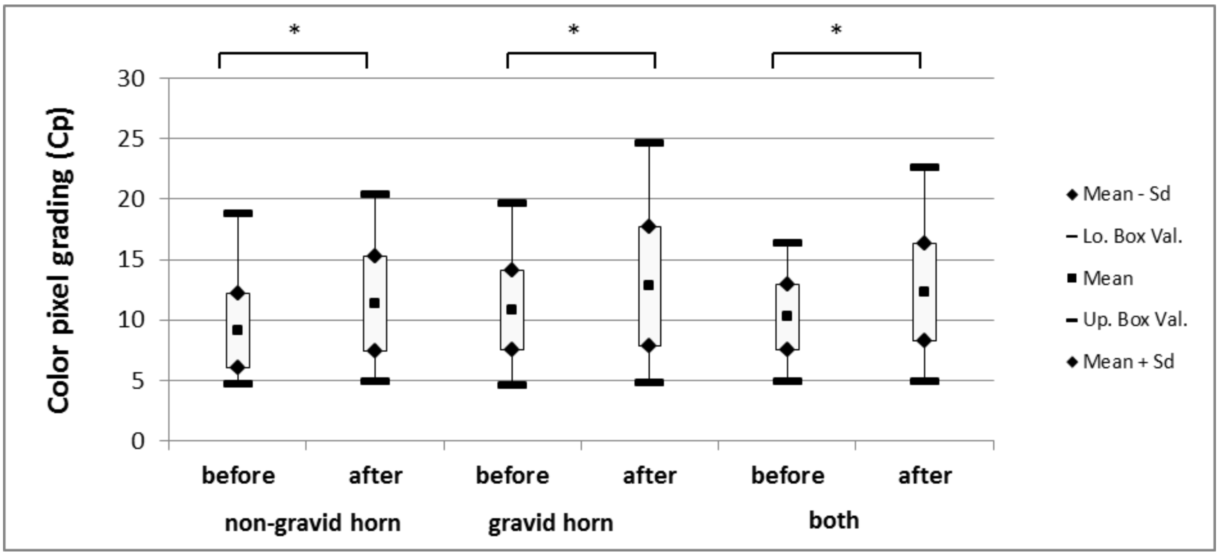

*
*
400
350
300
250
200
150
100
50
0
BFV (cm3/sec)
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd
before
after
before
after
non-gravid horn
gravid horn

6d

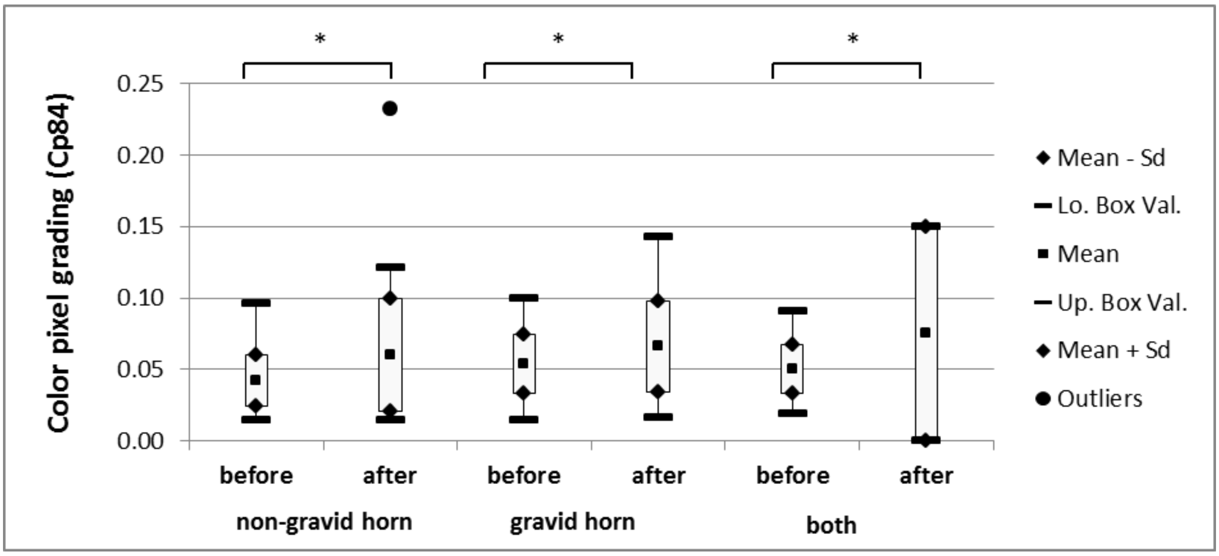
Fig. 7


*
*
*
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
rPP
before
after
before
after
before
after
non-gravid horn
gravid horn
both
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

7a


*
*
*
30
25
20
15
10
5
0
Color pixel grading (Cp)
before
after
before
after
before
after
non-gravid horn
gravid horn
both
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd

7b


*
*
*
Color pixel grading (Cp84)
0.25
0.20
0.15
0.10
0.05
0.00
before
after
before
after
before
after
non-gravid horn
gravid horn
both
Mean - Sd
Lo. Box Val.
Mean
Up. Box Val.
Mean + Sd
Outliers

7c

Legends to the Tables and Figures

Table 1: Correlation equation and coefficient of linear comparison of age and blood flow variables measured in the uterine arteries using Color Doppler sonography and placentomes using power-mode Doppler sonography in 8 cows, which ranged in age from 4 to 14 years.

Fig. 1: Placentome (1) imaged in power Doppler mode. The perfused portion appears in color (2) and is demarcated from the rest of the placentome. (3) Scale used to determine the RGB values.

Fig. 2: Mean and standard deviation of blood flow volume of the uterine arteries (■) and the color pixel grading in the placentomes (♦) in 8 cows in the last month of gestation. The arrow indicates parturition.
* indicates significant difference of blood flow volume of the uterine arteries between 4.5 and 0.5 weeks ante partum.

Fig. 3 a-f: Box and whisker plots of DM, RI, TAMV, BFV, relative placentome perfusion (rPP) and of the color pixel grading (Cp) of the ipsilateral and contralateral uterine arteries in 8 cows in the last month of gestation.
* indicates significant difference.

Fig. 4 a-b: Box and whisker plots of the TAMV and BFV in the contralateral and ipsilateral uterine arteries before and after epidural anesthesia with lidocaine in 8 cows in the last month of gestation.
* indicates a significant difference.

Fig. 5 a-c: Box and whisker plots of the relative placentome perfusion (rPP), color pixel grading (Cp) and color pixel grading from orange to yellow (Cp84) in the non-gravid and gravid uterine horns and for both horns combined before and after epidural anesthesia in 8 cows in the last month of gestation.
* indicates a significant difference.

Fig. 6 a-d: Box and whisker plots of the DM, RI, TAMV and BFV in the ipsilateral and contralateral uterine arteries before and after administration of isoxsuprine in 8 cows in the last month of gestation.
* indicates a significant difference.

Fig. 7 a-c: Box and whisker plots of the relative placentome perfusion (rPP), color pixel grading (Cp) and color pixel grading from orange to yellow (Cp84) in the non-gravid and gravid horns and both horns combined before and after the administration of isoxsuprine in 8 cows in the last month of gestation.

* indicates a significant difference.

Danksagung

An dieser Stelle möchte ich mich bei allen, die zum Gelingen dieser Arbeit beigetragen haben, ganz herzlich danken, insbesondere

Herrn Prof. Dr. U. Bleul für die Überlassung des Themas, die Übernahme des Referats, die stets grosse Hilfsbereitschaft und die unzähligen Ratschläge und Anregungen bis zur Fertigstellung der Arbeit.

Prof. Dr. M. Hässig und Prof. Dr. R. Bruckmaier für die Übernahme der Koautorenschaft.

Prof. Dr. Marco Hutter für die Erstellung des Auswertungsprogrammes.

Dr. Penelope Baloi für die Unterstützung bei ultrasonographischen Fragen.

Den Tierpflegerinnen und Tierpfleger des Departements für Nutztiere für die Betreuung der Kühe.

Meinen Kollegen aus dem Departement für Nutztiere für ihre Unterstützung, ihr Interesse, ihre wertvollen Tipps und Aufmunterungen.

Meinem Ehemann Stephan Kim, meiner Mutter Anna Egloff und meinen Freunden für ihre Unterstützung, die ermutigenden Worte und ihren Glauben an mich.

Circulum Vitae

Vorname, Name	Kim, Cornelia
Geburtsdatum	06. Mai 1982
Geburtsort	Baden AG
Nationalität	CH
Heimatort	Wettingen, AG
1989-1994	Primarschule Wettingen
1994-1997	Sekundarschule Wettingen
1997-1999	Bezirksschule Wettingen
1999- 2003	Kantonsschule Baden,CH,
2. Juli 2003	Maturitätsabschluss, Kantonsschule Baden, CH
September 2003- Oktober 2008	Studium der Veterinärmedizin, Universität Zürich, CH
20.Oktober 2008	Abschlussprüfung vet.med., Universität Zürich, CH
Mai 2010- November 2015	Anfertigung der Dissertation unter der Leitung von Prof. Dr. med. vet. U. Bleul am Departement für Nutztiere der Vetsuisse-Fakultät, Universität Zürich Direktor: Prof. Dr. Dr. h.c. U. Braun)
Oktober 2008 – April 2010	Arbeitsstelle in der Tierarztpraxis Rüdiger Endingen, AG
Mai 2010- September 2013	Assistenztierärztin am Departement für Nutztiere, Reproduktionsmedizin
Seit März 2014	Teilhaberin Tierarztpraxis Aesch GmbH, Wettingen AG